Dopamine Modulation of Hippocampal–Prefrontal Cortical Interaction Drives Memory-Guided Behavior

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Information gleaned from learning and memory processes is essential in guiding behavior toward a specific goal. However, the neural mechanisms that determine how these processes are effectively utilized to guide goal-directed behavior are unknown. Here, we show that rats utilize retrospective and prospective memory and flexible switching between these 2 memory processes to guide behaviors to obtain rewards. We found that retrospective memory is mainly processed in the hippocampus (HPC) but that this retrospective information must be incorporated within the prefrontal cortex (PFC) to be used to switch to an anticipatory response strategy involving prospective memory. Furthermore, switching between memory processes is regulated by the mesocortical dopamine (DA) system. Thus, DA D1 and D2 receptor activation in the PFC differentially affects retrospective memory processing within the HPC via an indirect feedback pathway. In contrast, D1, but not D2, receptor activation is crucial for incorporation of HPC-based retrospective information into the PFC. However, once this takes place, D2 receptor activation is required for further processing of information to effect preparation of future actions. These results provide a unique perspective on the mechanism of memory-based goal-directed behavior.

Keywords: dopamine, episodic memory, future planning, goal-directed behavior, hippocampus, prefrontal cortex

Introduction

Learning and memory processes are critical for an organism to effectively achieve goals, and developing an effective response strategy must include the ability to alter behavior whenever an obstacle is encountered. For example, when driving to work we may find our normal route blocked; we then would use retrospective memory to recall an alternate route. On the next day, remembering that the normal route is blocked, we would use a prospective planning strategy to take the alternate route and avoid a delay. The prefrontal cortex (PFC) and the hippocampus (HPC) are the 2 major brain regions proposed to mediate such learning and memory processes (Laroche et al. 2000; Simons and Spiers 2003; Takehara et al. 2003; Kesner and Rogers 2004; McDonald et al. 2004; Wiltgen et al. 2004). Indeed, individuals with neurological and psychiatric disorders including Alzheimer’s disease and schizophrenia that are known to exhibit pathology within the HPC and PFC show deficits in control of their behaviors based on memory processing (Perry and Hodges 1996; Frith 1997; Heckers et al. 1998; Buckner 2004; Shum et al. 2004; Meyer-Lindenberg et al. 2005; Jones et al. 2006).

Anatomical and electrophysiological studies have shown that the HPC and PFC exhibit reciprocal interactions. The HPC sends direct excitatory afferents into the PFC, targeting mainly the deep layers (layers V and VI), to contact both pyramidal neurons and interneurons (Sesack et al. 1989; Jay and Witter 1991). The PFC in turn sends feedback projections into the HPC (Fuster 1997). Although the PFC-recipient feedback into the HPC is indirect through the temporal cortex (Fuster 1997), a previous study has revealed that PFC lesion causes alterations of HPC neural activity associated with spatial localization in animals (i.e., place cells) (Kyd and Bilkey 2003), suggesting that such indirect PFC feedback information is indeed important for HPC function.

Accumulating evidence suggests that the mesocortical dopamine (DA) projection to the PFC plays a critical role in the modulation of information processing by HPC–PFC interactions. Thus, disconnection of DA-modulated HPC afferents into the PFC (via unilateral inactivation of the HPC combined with contralateral injection of DA D1 receptor antagonist into the PFC) disrupts working memory function (Seamans et al. 1998). Synaptic plasticity induction such as long-term potentiation (LTP) at HPC afferents into the PFC is also governed by D1 receptor activation and its interaction with N-methyl-o-aspartic acid channels (Gurden et al. 1999, 2000). In addition, a recent functional human imaging study has revealed that genetic variance of catechol-o-methyl transferase, a major molecule involved in clearance of DA in the PFC, affects HPC–PFC interactions during memory processing (Bertolino et al. 2006).

In this study, we use combined electrophysiological recordings and behavioral assessments in rats to provide evidence that the ability to utilize previous experience toward achievement of a specific goal is mediated by the DA-dependent exchange of information between the HPC and PFC. We hypothesize that such information exchange during memory processing is mediated by activation of DA D2 receptors in the HPC, which in turn facilitates information transfer back into the PFC.

Materials and Methods

Subjects

All experiments were conducted in accordance with the United States Public Health Services Guide for the Care and Use of Laboratory Animals and were approved by the University of Pittsburgh Institutional Animal Care and Use Committee. Male adult Sprague-Dawley rats were individually housed in cages in a temperature-controlled environment.

Behavioral Test

To test episodic memory and future planning strategies, we modified a task originally described in other studies (Kesner 1989). After 3 days of intensive handling (10 min each day) and another 3 days of habituation to an 8-arm radial maze, intracranial cannula implantation...
Field potential and single-unit signals were amplified 1000 times and 10 000 times with an AC amplifier and band-pass filtered at 0.1-100 Hz and 100-10 000 Hz, respectively. Recordings were digitized with an interface board at 10 kHz and fed to a computer for off-line analysis. All data handling was performed using custom software (Neuroscope). Criteria for acceptable single-unit sampling was defined as a signal-to-noise ratio of 3:1 or greater and at least 5 min of stable recording.

Concentric bipolar stimulation electrodes were placed in the HPC (dorsal CA1) or superficial layers of the PFC (AP, −3.0 mm; L, +0.2 mm; DW, +2.4 mm) in the plasticity experiments. Single current pulses were delivered every 5 s to the HPC (0.2 ms; 0.2-0.8 mA) or the PFC (0.2 ms; 0.05-0.2 mA) for test pulses. Current intensity was adjusted to evoke approximately 50-60% of maximal responses. Two types of tetanic stimulation were used to induce short-term potentiation (STP). Theta burst stimulation consisted of 3, 4, or 5 trains of stimuli at 7 Hz (30, 40, or 50) with each train composed of 3 pulses at 100 Hz and given into the dorsal CA1. The other tetanic stimulation consisted of either 2 or 3 trains of stimuli at 1 Hz (2 or 3) with each train composed of 5 pulses at 40 Hz and given within the PFC. Changes in amplitudes of the potentials beginning 1 ms before the test pulse stimulation up to the first peak of negative (with HPC stimulation) or positive (with intra-PFC stimulation) shifts of evoked field potentials were measured before and after tetanization.

Drugs were administered intraperitoneally or locally into the PFC via reverse microdialysis. Dialysis probes (2-mm exposed membrane) were advanced slowly into the PFC at the rate of 3-5 μm/s to minimize any damage of brain tissues. All drugs were purchased from Sigma (St Louis, MO) and were dissolved in aCSF (SKF38393, 10 μM; SCH23390, 10 μM; quinpirole, 10 μM; eticlopride, 20 μM) (Goto and Grace 2005). aCSF was continuously perfused throughout the experiments and switched to drug administration during recordings. The D1 and D2 antagonists (SCH23390, 0.5 mg/kg; eticlopride, 1.0 mg/kg, dissolved in 1 mL aCSF) were also systemically administered 5 min before recordings were started.

Results

Flexible Utilization of Memory Processing in Goal-Directed Behavior

The ability of rats to use memory processes to appropriately guide their behaviors toward a specific goal was tested using a modified 8-arm radial maze task (Fig. 1A) (Kesner 1989). As described in the Materials and Methods, 1-, 3-, 5-, or 7-arms were presented to rats first and after 5 min of delay, 2-arms were presented, one that rats had entered and the other that they had not. Animals were required to choose the unentered arm to obtain rewards. When control animals were previously exposed to 1-arm, they correctly chose the unentered arms 83.3 ± 7.5% (mean ± standard deviation [SD]) of the time (n = 6; Fig. 1B). This percentage declined as the number of preexposed arms increased (73.6 ± 9.7 and 57.0 ± 15.3% at 3- and 5-arms, respectively; P = 0.002 comparing between 1- and 5-arm conditions, 1-way ANOVA with post hoc Tukey test; Fig. 1B). However, the percentage of correct responses was significantly increased when rats had been preexposed to the 7-arm condition (84.7 ± 8.2%; P = 0.001 comparing between 5- and 7-arm conditions; Fig. 1B), suggesting that animals switched their response strategies between the 5- and 7-arm conditions. One explanation for these results is that animals might have taken into account the arms that they had entered previously to choose subsequent responses under the 1-, 3-, and 5-arm conditions. This is evidenced by the decline in the percentages of correct responses as the number of arms presented was increased. In contrast, in the 7-arm condition, animals may have utilized a more efficient response strategy from those used in the 1-, 3-, and 5-arm conditions; for example, one possible
explanation would be that, under this condition, the animals might extrapolate prospectively which arm that they were going to enter for subsequent responses. This would be consistent with the observation that the percentage of correct responses in the 7-arm condition was similar to that in the 1-arm condition. Another potential explanation for these results is that animals might utilize spatial cues to solve the behavioral task rather than utilizing retrospective and prospective memory. However, if this were the case, the behavior of the animal would be inordinately influenced by precisely which arms are presented in the test phase; for example, if the correct and incorrect arms presented are spatially far apart or located in close proximity to each other. Nevertheless, we found that correct responses were not influenced by the pattern of arm presentation.

**HPC-PFC Interactions in Memory Processing**

To test the dependence of HPC-PFC interactions that may underlie the flexible utilization of memory processing, muscimol was infused 1) bilaterally into the dorsal HPC, 2) bilaterally into the dorsal portion of the medial PFC, and 3) unilaterally into the HPC and contralaterally into the PFC. Inactivation of the HPC resulted in disruption of performance in both the 1- and 7-arm conditions (59.7 ± 9.7% in 1-arm; $P = 0.024$ compared with control, 2-way ANOVA with post hoc Tukey test; 52.8 ± 10.1% in 7-arm; $P = 0.003; n = 6$; Fig. 2A), whereas PFC inactivation impaired performance in the 7-arm but not the 1-, 3-, and 5-arm conditions (54.2 ± 8.7% in 7-arm; $P = 0.006; n = 6$; Fig. 2B). In contrast, when the HPC and PFC were disconnected by contralateral infusions, the animals exhibit impairment only in the 7-arm condition (52.8 ± 6.8% in 7-arm; $P = 0.003; n = 6$; Fig. 2C). These results suggest that a response strategy used in the 1-, 3-, and 5-arm conditions involved information processing primarily in the HPC and that HPC-based information could be incorporated in the PFC to provide the basis for switching to a new response strategy in the 7-arm condition.

**Different Roles of D1 and D2 Activation in Memory Processing**

We next investigated the role of the mesocortical DA system in this flexible utilization of response strategies in guiding goal-directed behaviors using local infusion of D1 and D2 agonists and antagonists into the PFC. Local infusion of the D1 agonist SKF38393 facilitated performance at the 5-arm condition (75.0 ± 9.1% in 5-arm; $P = 0.005; n = 6$; Fig. 3A), whereas the D2 agonist quinpirole impaired performance at the 1- and 3-arm conditions (57.0 ± 8.2% in 1-arm; $P = 0.008; 45.9 ± 6.9%$ in 3-arm; $P = 0.004; n = 6$; Fig. 3B) but facilitated performance at the 5-arm condition (80.5 ± 4.3% in 5-arm; $P = 0.005; n = 6$; Fig. 3B). These drugs were infused into the PFC yet affected HPC-mediated information processing, suggesting that D1 and D2 receptor activation in the PFC differentially affects HPC activity that mediates retrospective memory processes, possibly via indirect projections from the PFC to the HPC (Fuster 1997; Kyd and Bilkey 2003). Improved correct responses in the 5-arm condition were observed following both D1 and D2 agonist infusion. However, the mechanism of these improvements seems to be different. Improvement of performance in the 5-arm condition with D1 agonist may be simply due to facilitation of information processing in the HPC provided by PFC feedback. In contrast, impaired performance at the 1- and 3-arm conditions but improved performance at the 5-arm condition with the D2 agonist suggest that D2 receptor activation in the PFC might interfere with HPC activity, possibly via the feedback projection from the PFC to the HPC. Thus, one possible explanation is that D2 receptor activation in the PFC could facilitate processing of a response strategy that is normally

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Figure 1. Description of behavioral task. (A) Schematic diagram illustrating the behavioral test. ITI: intertrial interval. (B) Bar graph showing percentages of correct responses at the 1-, 3-, 5-, and 7-arm conditions. Higher correct responses were observed at the 1- and 7-arm conditions, suggesting that animals utilized retrospective and prospective memory in each condition, respectively (1-way ANOVA with post hoc Tukey test, *$P < 0.01$). Error bars in this and all other figures indicate SD.
utilized only in the 7-arm condition, so that animals might have already switched their response strategy in the 5-arm condition.

Administration of either the D1 antagonist SCH23390 or the D2 antagonist eticlopride into the PFC impaired performance in the 7-arm condition without affecting other arm conditions (62.5 ± 15.6% with SCH23390; \( P = 0.012; n = 6 \); 63.9 ± 11.4% with eticlopride; \( P = 0.028; n = 6 \); Fig. 3C,D), suggesting that the D1 and D2 antagonists affect HPC \( \rightarrow \) PFC information processing, and coactivation of D1 and D2 receptors in the PFC are required for utilization of HPC-based retrospective information to switch a response strategy in the 7-arm condition.

**D1 and D2 Regulation of Reciprocal HPC-PFC Interactions**

The mechanisms underlying how D1 and D2 activation in the PFC regulate switching of response strategies were further examined using in vivo electrophysiological recordings. Local administration of the D1 and D2 agonists into the PFC via microdialysis probes produced significant augmentation and attenuation of HPC neuron spike firing frequency, respectively (185.9 ± 212.8% increase with SKF38393, \( P = 0.028 \) comparing before and after drug administration, paired \( t \)-test; \( n = 9 \); 45.8 ± 26.8% decrease with quinpirole, \( P = 0.008; n = 9 \); Fig. 4A,B). In contrast, administration of the D1 and D2 antagonists into the PFC inactivation

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**Figure 2.** Disruption of HPC-PFC interactions altered the processing of retrospective and prospective memory. (A) Bilateral HPC inactivation disrupted performance at both the 1- and 7-arm conditions. (B) Bilateral PFC inactivation disrupted performance only at the 7-arm condition. (C) Unilateral PFC and contralateral HPC inactivation induced impairments similar to those produced by bilateral PFC inactivation (2-way ANOVA with post hoc Tukey test, \( **P < 0.05, *P < 0.01 \)).

**Figure 3.** Altering DA stimulation within the PFC produces selective actions on the processing of retrospective and prospective memory. (A) Infusion of the D1 agonist SKF38393 (SKF) into the PFC selectively improved correct responses at the 5-arm condition. (B) The D2 agonist quinpirole (QIN) disrupted performance at the 1- and 3-arm conditions but improved correct responses at the 5-arm condition. (C) The D1 antagonist SCH23390 (SCH) produced an impairment of performance at the 7-arm condition. (D) Similarly, the D2 antagonist eticlopride (ETI) also disrupted performance at the 7-arm condition (2-way ANOVA with post hoc Tukey test, \( *P < 0.01, **P < 0.05 \)).
PFC did not significantly alter HPC neuron spike firing (9.6 ± 25.7% increase with SCH23390; n = 6; 11.2 ± 40.1% increase with eticlopride; n = 7; Fig. 4A,B). These results suggest that activation of D1 and D2 receptors in the PFC affected neural activities in the HPC via the PFC → HPC indirect pathway.

We also evaluated DA-dependent synaptic plasticity in the PFC to elucidate the effects of the D1 and D2 antagonists on HPC → PFC information processing. Previous studies have shown that HPC activation induces endogenous DA release in the PFC (Peleg-Raibstein et al. 2005) and DA-dependent LTP at HPC afferents into the PFC (Gurden et al. 1999). In addition, recent studies have reported a coupling of PFC activities with HPC theta oscillations during cognitive task performance (Hyman et al. 2005; Siapas et al. 2005). Thus, we tested the effect of theta burst stimulation of the HPC on the induction of synaptic plasticity at these afferents into the PFC. We found that moderate strengths (4 or 5 trains of stimulation given at 7 Hz, 1 train consisting of 3 pulses at 100 Hz) of theta burst stimulation induced STP of the amplitudes of evoked field potentials in the PFC that persisted for longer than 5 min (74.5 ± 8.6% and 33.2 ± 11.6% increase at 0 and 5 min after 4 theta tetanic stimulation; n = 8; Fig. 5A), which is the duration of a delay implemented in the behavioral test that we employed. This theta burst-induced STP was significantly attenuated by intraperitoneal administration of the D1 antagonist SCH23390 (0.5 mg/kg; 38.4 ± 18.6% increase at 0 min after 4 theta tetanic stimulation; P = 0.012 compared with normal condition, 2-way ANOVA with post hoc Tukey test; 5.3 ± 13.9% at 5 min after; P = 0.009; n = 8; Fig. 5B,C) but not by the D2 antagonist eticlopride (1.0 mg/kg; 89.3 ± 11.4% and 29.1 ± 12.4% increase at 0 and 5 min after 4 theta tetanic stimulation; n = 8; Fig. 5B,C), suggesting that D1, but not D2, activation is critical for HPC → PFC information processing.

The role of D2 activation on synaptic plasticity in the PFC was further examined using intra-PFC stimulation. Theta burst stimulation delivered to the superficial layer had only weak effects on STP obtained in the deep layer of the PFC (Fig. 5D). Even the strongest theta burst stimulation employed (5 trains) induced only a transient increase in the evoked field potentials, and this decayed within 5 min. In contrast, when the PFC was stimulated using a train of pulses at 40 Hz (2 or 3 trains of stimulation given at 1 Hz, 1 train consisting of 5 pulses at 40 Hz), which is in the range of the gamma frequency, the STP that was induced persisted for a duration of more than 5 min, which was similar to that observed with theta burst stimulation in the HPC (93.9 ± 9.9% and 50.5 ± 9.5% increase at 0 and 5 min after 3 gamma tetanic stimulation; n = 8; Fig. 5D). The STP induced by intra-PFC stimulation was significantly attenuated by systemic administration of the D2 antagonist (39.8 ± 7.2% [P = 0.002] and 2.3 ± 13.8% [P = 0.003] increase at 0 and 5 min after 3 gamma tetanic stimulation; n = 7; Fig. 5E,F), although the D1 antagonist also moderately attenuated STP at 0 min (52.2 ± 10.2% increase; P = 0.009; n = 9; Fig. 5E,F) and 5 min (35.0 ± 12.6% increase; P = 0.030; Fig. 5E,F) after tetanic stimulation. These results suggest that short-term synaptic plasticity induced at HPC afferents to the PFC either directly or via local circuits within the PFC are differentially regulated by D1 and D2 receptor activation.

Discussion

Our data support the contention that the choice between different response strategies that utilize distinct memory processes is mediated by bidirectional interactions between the HPC and PFC and that flexibility in utilizing these response strategies is dependent on mesocortical DA activation. Thus, our study suggests that retrospective memory is dependent on the HPC but that such retrospective information has to be incorporated into the PFC in order to enable prospective information processing for anticipation of future actions. Furthermore, selection of HPC-dependent retrospective information appears to depend on D1, but not D2, receptor stimulation in the PFC. Thus, we found that D2 receptor activation impairs prospective memory processing, suggesting that retrospective memory is processed independent from D2 receptor activation, but if D2 receptors are indeed activated, then it is disrupted. In contrast, the ability to generate prospective planning-like strategies based on this retrospective HPC information is largely dependent on D2 receptor modulation of PFC intrinsic circuits. This is consistent with previous results by others in which D2 receptor stimulation in the PFC is proposed to facilitate behavioral flexibility (Mehta et al. 2004; Seamans and Yang 2004; Winterer and Weinberger 2004; Floresco et al. 2006; Tost et al. 2006).

A number of possible explanations could be made for observations of memory-guided response strategies to account for the behavior of the animals tested in this study. One potential scenario would be that these animals utilize a retrospective information-processing mechanism similar to episodic memory for guiding their behaviors in the 1-, 3-, and 5-arm conditions, whereas their response strategy would switch at the 7-arm condition to a mechanism that may be similar to...
planning of future actions. Indeed, some other studies have shown that animals can utilize similar retrospective and prospective memory functions in driving goal-directed behavior (Ingvar 1985; Squire 1992; Rainer et al. 1999; Mulder et al. 2000; Eichenbaum 2001; Fortin et al. 2002; Dragoi and Buzsaki 2006; Mushiake et al. 2006). Electrophysiological recordings in rodents and primates have shown that sustained spike firing during the delay period of working memory serves to encode prospective information such as planned future responses at the level of PFC neurons (Ingvar 1985; Rainer et al. 1999; Mulder et al. 2000; Eichenbaum 2001; Fortin et al. 2002). In contrast, a lesion of the HPC disrupts episodic memory function in humans and rodents (Squire 1992; Eichenbaum 2001; Fortin et al. 2002), and moreover, a recent study has shown that assemblies of HPC neurons encode episodic memory (Dragoi and Buzsaki 2006). Our study provides a new viewpoint suggesting that bidirectional interactions between the HPC and PFC may be essential for mediating the behaviorally relevant spike pattern associated with the ability of the HPC and PFC to optimally utilize retrospective and prospective memory processes.

The PFC expresses both DA D1 and D2 receptors (Vincent et al. 1993), and D1-dependent, but not D2-dependent, HPC–PFC interactions have been described in previous studies. Thus, disconnection of HPC–PFC interactions via unilateral D1 antagonist infusion into the PFC combined with activation of the contralateral HPC disrupts working memory (Seamans et al. 1998). Similarly, synaptic plasticity such as LTP induction at HPC afferents into the PFC is selectively dependent on D1 activation (Gurden et al. 2000). On the other hand, the function of D2 receptors in the PFC is relatively unclear. Nevertheless, a similar long-term synaptic plasticity induced within the PFC networks by stimulation of the superficial layers, where corticocortical afferents are located, requires both D1 and D2 activation (Matsuda et al. 2006). These data suggest that different cellular mechanisms may underlie the induction of synaptic plasticity in the PFC network, in which DA receptor subtypes play distinct roles depending upon which afferent such synaptic plasticity is induced. Indeed, in support of this model of functional segregation, a recent study in primates shows that D1 and D2 receptor antagonists affect different aspects of PFC neuronal activity during working memory (Wang et al. 2004). Our study is consistent with these previous findings in which D1, but not D2, activation modulates STP at HPC inputs, whereas D2 activation modulates STP induced within the PFC network. Thus, it appears that DA exerts its effects via a 2-step process: D1 receptors select the information from the HPC that is to be incorporated into the PFC network. This incorporated information is further processed within the PFC by D2 receptors (Fig. 6A). Based on these results, we propose that increased DA release that is sufficient to stimulate both D1 and D2 receptors may be required to utilize future planning strategies (Fig. 6B). D1 activation could facilitate the
use of episodic memory by facilitating PFC feedback onto the HPC via an indirect pathway, whereas D2 receptor activation could trigger a switch from the use of HPC-based episodic memory to a PFC-based employment of future planning strategies via suppression of HPC activity.

Deficits in both episodic memory and future planning are observed in disorders such as Alzheimer’s disease and schizophrenia, disorders that are also known to exhibit structural and functional abnormalities in the HPC and PFC (Perry and Hodges 1996; Frith 1997; Heckers et al. 1998; Buckner 2004; Shum et al. 2004; Meyer-Lindenberg et al. 2005; Jones et al. 2006). Moreover, impairments of functional connectivity between the PFC and limbic structures (Frith 1997; Meyer-Lindenberg et al. 2005) and its modulation by the DA system (Smolka et al. 2005) have been described specifically in schizophrenia. Considered in light of the current results, deficits in the flexible utilization of episodic memory and future planning observed in these disorders may be a direct consequence of impairment of limbic and PFC interactions and their modulation by the DA system.

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